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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,229	01/23/2002	Jose Remacle	VANM213.001CP1	6914

20995 7590 02/25/2003

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EXAMINER	
SPIEGLER, ALEXANDER H	

ART UNIT	PAPER NUMBER
2637	12

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,229	REMACLE ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[·] Responsive to communication(s) filed on *December 6th, 2002* .

2a)[ ] This action is **FINAL**. 2b)[×] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[·] Claim(s) *1-79* is/are pending in the application.

4a) Of the above claim(s) *62-79* is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[·] Claim(s) *1-61* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[·] The drawing(s) filed on *6/26/02* is/are: a)[×] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[·] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[×] None of:

1.[×] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[·] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [×] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [×] Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,9* .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-61) in Paper No. 11, filed on December 6th, 2002 is acknowledged.

Specification

2. Claim 3 recites, "wehrein", which could be amended to recite "wherein".

Drawings

3. This application has been filed with informal drawings, which are acceptable for examination purposes only. Formal drawings will be required if the application is allowed.

Information Disclosure Statement

4. The information disclosure statement of Paper Nos. 6 and 9, comply with CFR 1.97, 1.98 and M.P.E.P. 609, and has been considered.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-61 over "components thereof" because it is not clear as to what constitutes "components thereof" or "components" of an organism. The specification does not teach what is encompassed by a "component thereof". Does this term encompass any of the possible

components of an organism, such as sugars, fatty acids, proteins, hair, etc.? It is suggested that the claim be amended to delete "component thereof" or "component". It is noted that claim 9 refers to "the components to detect are nucleotide sequences amplified or copied as targets to be hybridized" and claims 50-54 recite different receptors as "components", however these claim limitations do not provide a clear definition of what is to be encompassed by "components".

B) Claim 4 is indefinite over "original components" because it is not clear as what constitutes an "original component". The specification does not define this term, and in a search of US patents, "original component" was not found to be in the same sentence as "organism" in any patents that have issued by February 18, 2003.

C) Claims 10-11 are indefinite over "first category" and "second category" because these recitations lack antecedent basis, because claim 1 does not refer to a "first" or "second category" of capture molecules.

D) Claims 46-47 and 55 are indefinite over "the microorganism" because this recitation lacks antecedent basis, because claim 1 does not recite "microorganism".

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

8. Claims 1-7, 9-34 39-45 and 55-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. (USPN 5,807,522).

Due to the lack of clarity of the claims, the claims have been interpreted as drawn to methods of identifying and/or quantifying an organism or part of an organism by hybridizing a target to capture molecule bound on an array, wherein the array has a density of at least 4 different bound single stranded capture nucleotide sequences/cm^2.

Brown teaches the use of microarrays of biological samples comprising capture molecules immobilized on said microarray in DNA hybridization assays, monitoring of gene expression, genetic diagnosis, genotyping of organisms, identification of microorganisms, etc. (col. 1, ln. 15-19, col. 14, ln. 35 to col. 15, ln. 67 and Example 3).

Brown teaches:

"In another aspect, the invention includes a substrate with a surface having *a microarray of at least 10^3 distinct polynucleotide or polypeptide biopolymers in a surface area of less than about 1 cm^2*. Each distinct biopolymer (i) is disposed at a separate, defined position in said array, (ii) has a length of at least 50 subunits, and (iii) is present in a defined amount between about 0.1 femtomoles and 100 nanomoles.

In one embodiment, *the surface is glass slide surface coated with a polycationic polymer, such as polylysine, and the biopolymers are polynucleotides*. In another embodiment, the substrate has a water-impermeable backing, a water-permeable film formed on the backing, and a grid formed on the film. The grid is composed of intersecting water-impervious grid elements extending from said backing to positions raised above the surface of said film, and partitions the film into a plurality of water-impervious cells. *A biopolymer array is formed within each well.*

More generally, there is provided *a substrate for use in detecting binding of labeled polynucleotides to one or more of a plurality different-sequence, immobilized polynucleotides.* The substrate includes, in one aspect, a glass support, a coating of a polycationic polymer, such as polylysine, on said surface of the support, and an array of distinct polynucleotides electrostatically bound non-covalently to said coating, where each distinct biopolymer is disposed at a separate, defined position in a surface array of polynucleotides.

Also forming part of the invention is a method of detecting differential expression of each of a plurality of genes in a first cell type, with respect to expression of the same genes in a second cell type. In practicing the method, there is first produced fluorescent-labeled cDNAs from mRNAs isolated from the two cells types, where the cDNAs from the first and second cell types are labeled with first and second different fluorescent reporters.

A mixture of the labeled cDNAs from the two cell types is added to an array of polynucleotides representing a plurality of known genes derived from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array. The array is then examined by fluorescence under fluorescence excitation conditions in which (i) polynucleotides in the array that are hybridized predominantly to cDNAs derived from one of the first or second cell types give a distinct first or second fluorescence emission color, respectively, and (ii) polynucleotides in the array that are hybridized to substantially equal numbers of cDNAs derived from the first and second cell types give a distinct combined fluorescence emission color, respectively. The relative expression of known genes in the two cell types can then be determined by the observed fluorescence emission color of each spot." (col. 4)

Brown also teaches the target nucleotide sequence can amplified prior to being hybridized to the capture nucleotide sequences on an array (col. 15), and that the target can be a microorganism (Example 1). Additionally, Brown teaches the many possible embodiments of the microarray and its methods of detection, especially the use of a hybridization signal for detection, the components to be detected can be amplified by PCR prior to hybridization, or can be mRNA, which is retrotranscribed into cDNA prior to hybridization (col. 12-14 and Examples 1-3). With respect to claims 2-3 and 7, Brown teaches that at least 2 or 4 "related" components are among the organism or component sample (see Examples 1-2: Example 1 teaching the hybridization of 16 chromosomes of *S. cerevisiae* and Example 2 teaching the hybridization of different species of Arabidopsis).

9. Claims 1-34, 37, 39-45, 47 and 55-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Gingeras et al. (USPN 6,228,575).

Gingeras teaches methods for speciating and phenotyping organisms by using oligonucleotide based microarrays.

Specifically, Gingeras teaches methods for identifying species of Mycobacterium comprising:

"(a) hybridizing a sample comprising the target nucleic acid or a subsequence thereof to an array of oligonucleotide probes immobilized on a solid support, the array comprising:

a first probe set comprising a plurality of probes, each probe comprising a segment of nucleotides exactly complementary to a subsequence of the reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence, wherein each interrogation position corresponds to a nucleotide position in the reference or target sequence;

(b) determining a hybridization intensity from each probe;

(c) plotting the hybridization intensities versus the nucleotide position corresponding to the probe from which the hybridization intensity was determined to derive a target plot of hybridization intensity;

(d) repeating steps (a)-(c) with the target sequence replaced by the reference sequence, to derive a baseline plot of the reference sequence; and

(e) comparing the target plot to the baseline plot to identify the genotype and/or phenotype of the organism.

Another aspect of the invention provides an array of oligonucleotide probes immobilized on a solid support, the array comprising: a first probe set comprising a plurality of probes, each probe comprising a segment of nucleotides exactly complementary to a subsequence of a reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence" (col. 3).

Gingeras also teaches:

- It is "desirable to amplify the nucleic acid prior to hybridization," and that the target sample may be labeled (col. 8, ln. 34-58).
- The differing probes used on the array comprise probes specific individual target components or their sub-groups and probes being specific for all the components of the group (col. 9, 13-16).

- This methodology is applicable to other microorganisms, reference sequences and mRNA (col. 8 and 12).
- This method can discriminate more than 4 related species (col. 21-23 and 32-46).
- The array has a density of at least 60 different oligonucleotides/1 cm^2.
- Single nucleotide polymorphisms can be detected (col. 29-30).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 8, 35-38, 46-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (USPN 5,807,522), as applied to claims 1-7, 9-34 39-45 and 55-61 above, and further in view of Vannuffel et al. (WO 99/16780, cited in the IDS).

The teachings of Brown are presented above. Specifically, Brown teaches methods of identifying and/or quantifying an organism or part of an organism by hybridizing labeled target sequences to capture nucleotide sequences on an array, wherein the array has a density of at least 4 different bound single stranded capture nucleotide sequences/cm^2. Brown does not teach the specific detection of Staphylococci species using a consensus sequence from the *Staphlococcus* genus and a specific *Staphlococcus* species probes for detection.

However, Vannuffel teaches the specific detection of Staphylococci species using consensus sequences from the *femA Staphlococcus* nucleotide sequence and *Staphlococcus*

species specific probes (see abstract, pgs. 4-5, 8-13 and Examples 1-7). More specifically, Vannuffel teaches a method for identification and/or quantification of staphylococcal species comprising, obtaining a Staphyoloccal species from a biological sample, possibly purifying and amplifying said sample, and then identifying said species through hybridization on an oligonucleotide array, wherein the consensus and specific sequences of *femA* are used as capture nucleotide sequences (pgs. 11-12). Vannuffel also teaches that the method can be advantageously combined with another specific detection step of possible resistance to antibiotics (pg. 11). Vannuffel also teaches that the probes of the invention can be immobilized on any solid support suitable for fixation of a nucleic acid (pgs. 12-13). Vannuffell teaches that the invention can detect several Staphyoloccal species, such as *S. hominis, S. saprophyticus, S. epidermidis and S. haemolyticus* (pg. 4), and other gram-positive bacteria (pgs. 5 and 10).

In view of the teachings of Vannuffel, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Brown so as to have included the consensus sequences (i.e. primers and probes) specific for the *femA* sequence of Staphylococcal species, in order to have achieved the benefit of providing an effective means of detecting specific species of the Staphylococci genus for use in diagnosing staphylococcal infections.

12. Claims 35-36, 38, 46, 48-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gingeras et al. (USPN 6,228,575), as applied to claims 1-34, 37, 39-45, 47 and 55-61 above, and further in view of Vannuffel et al. (WO 99/16780, cited in the IDS).

The teachings of Gingeras are presented above. Specifically, Gingeras each teaches

methods of identifying and/or quantifying an organism or part of an organism by hybridizing labeled target sequences to capture nucleotide sequences on an array, wherein the array has a density of at least 4 different bound single stranded capture nucleotide sequences/cm^2. Gingeras does not teach the specific detection of Staphylococci species using a consensus sequence from the *Staphlococcus* genus and a specific *Staphlococcus* species probes for detection.

However, Vannuffel teaches the specific detection of Staphylococci species using consensus sequences from the *femA Staphlococcus* nucleotide sequence and *Staphlococcus* species specific probes (see abstract, pgs. 4-5, 8-13 and Examples 1-7). More specifically, Vannuffel teaches a method for identification and/or quantification of staphylococcal species comprising, obtaining a Staphyoloccal species from a biological sample, possibly purifying and amplifying said sample, and then identifying said species through hybridization on an oligonucleotide array, wherein the consensus and specific sequences of *femA* are used as capture nucleotide sequences (pgs. 11-12). Vannuffel also teaches that the method can be advantageously combined with another specific detection step of possible resistance to antibiotics (pg. 11). Vannuffel also teaches that the probes of the invention can be immobilized on any solid support suitable for fixation of a nucleic acid (pgs. 12-13). Vannuffell teaches that the invention can detect several Staphyoloccal species, such as *S. hominis, S. saprophyticus, S. epidermidis and S. haemolyticus* (pg. 4), and other gram-positive bacteria (pgs. 5 and 10).

In view of the teachings of Vannuffel, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gingeras so as to have included the consensus sequences (i.e. primers and probes) specific for the *femA* sequence of Staphylococcal species, in order to have achieved the benefit of providing an effective means

of detecting specific species of the Staphylococci genus for use in diagnosing staphylococcal infections.

Conclusion

13. No claims are allowable.

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Balch et al. (USPN 6,331,441)

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
February 20, 2003

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
2/20/03